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(21) International Application Number: PCT/SE99/00049 (22) International Filing Date: 15 January 1999 (15.01.99) (30) Priority Data: 9800170-4 22 January 1998 (22.01.98) SE 9800766-9 9 March 1998 (09.03.98) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): FLINK, Ola [SE/SE]; Astra Arcus AB, S-151 85 Södertälje (SE). PETRÉN, Sven [SE/SE]; Astra Arcus AB, S-151 85 Södertälje (SE). (74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S-151 85 Södertälje (SE).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: PHARMACEUTICAL FORMULATION COMPRISING AN ANTIBODY AND A CITRATE BUFFER (57) Abstract <p>The present invention relates to an isotonic pharmaceutical formulation comprising an antibody and a buffer, wherein the antibody is present at 0.5 mg/ml to 10 mg/ml, the buffer is a citrate buffer present at 5 mmol/l to 20 mmol/l and the pH of the formulation is 5.3 to 7.2. The invention also relates to a method for the storage of antibodies by use of such formulations and to the use of such formulations in therapy.</p>		

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PHARMACEUTICAL FORMULATION COMPRISING AN ANTIBODY AND A CITRATE BUFFER

The invention relates generally to antibody formulations and particularly to stabilised
5 antibody formulations for storage and for therapeutic administration.

Purified proteins, particularly those produced using recombinant DNA technology are now
well established as pharmaceutical agents. Such proteins do however present a range of
problems associated with their stable formulation. Many protein preparations are
10 particularly unstable in dilute solutions and must be formulated in such a way as to prevent
significant levels of denaturation, agglomeration or degradation. These problems are
particularly acute in the formulation of large proteins such as immunoglobulins.

Immunoglobulins or antibodies are known to be prone to form aggregates and particulates
in solution and this has long provided special problems in generating suitable formulations
15 for the storage and administration of therapeutic antibodies. Existing antibody formulations
frequently require to be filtered before injection to remove aggregates or particulate matter
which is inconvenient and tends to reduce the accuracy of the injected dose.

Various attempts have been made to overcome the problems of antibody formulation:
20

EP 0 073 371 describes intravenously administrable immunoglobulin compositions which
have their pH adjusted to 3.5 to 5.0 as proteins are known to be more stable at low pH.
Such low pHs however tend to result in undesirable reactions at the site of injection .

25 US 4650772 describes a method for stabilising thermally unstable monoclonal antibodies
which requires the presence of 0.25% to 5% hydrolysed ovalbumin. The use of ovalbumin
in pharmaceutical formulations results in the induction of an allergic response which
prevents its effective use for repeated administrations.

30 WO 90/11091 describes the use of maltose and buffers in a lyophilised formulation of
monoclonal antibodies. Lyophilisation is however an expensive process and the need to

resuspend the formulation prior to administration adds to the complexity of the treatment regimen. It was suggested that citrate buffer may be used to buffer the pH at between 3.0 and 6.0.

5 The present invention provides a more simple antibody formulation than those presently known, providing a formulation which is both suitable for administration and has improved storage properties. Existing antibody formulations require the use both of a stabiliser and of a buffer. However antibodies in formulations of the present invention are stabilised only by citrate buffer in a saline solution at a physiologically preferable pH.

10

There is therefore provided according to the present invention, an isotonic pharmaceutical formulation comprising an antibody and a buffer, wherein the antibody is present at 0.5mg/ml to 10mg/ml, the buffer is a citrate buffer present at 5mmol/l to 20mmol/l and the pH of the formulation is 5.3 to 7.2.

15

A citrate buffer for use in the present invention may be generated by dissolution of free citric acid or preferably a pharmaceutically acceptable salt of citrate, preferably a sodium salt.

20 A formulation of the present invention may be generated by solubilising the relevant antibody, preferably in saline and adding an amount of citrate buffer necessary to obtain a pH of the solution in the range 5.3 to 7.2. The citrate buffer is preferably present at 5mmol/l to 20mmol/l.

25 A formulation of the present invention may additionally contain other substances desirable for therapeutic efficacy of the antibody e.g. chelators, or other therapeutic compounds desirable to be coformulated with the antibody but it is preferably substantially free of any additional compound known for use in antibody stabilising e.g. Tween, mannitol or maltose. By 'substantially free' it is meant that such additional compounds known for use in
30 antibody stabilising formulations may not be present in formulations of the present

invention in an amount capable alone or in combination with one or more other stabilisers, of having a stabilising effect upon an antibody in a formulation.

In preferred embodiments of the present invention citrate buffer is present in the formulation at 7.5mmol/l to 15mmol/l and most preferably at 10mmol/l. Any pharmaceutically acceptable citrate buffer may be used in the present invention but the citrate buffer is preferably sodium citrate. It is more preferable that sodium citrate dihydrate is used and most preferable that the citrate buffer be generated from a mixture of sodium citrate dihydrate and citric acid monohydrate. In the preferred embodiments of the present invention, the formulation contains about 2.4 mg/ml sodium citrate dihydrate and about 0.387 mg/ml citric acid monohydrate.

The present invention is suitable for the formulation of any antibody or antibody fragment. Any reference to an antibody herein will be taken to include a fragment of such antibody.

The antibody for use in a formulation of the present invention may be natural or recombinant and may be generated according to any known technique. Natural antibodies may be those isolated either by purification from body fluids or from cell lines and may be polyclonal or monoclonal antibodies. Particularly preferred antibodies for use in formulations of the present invention are recombinant antibodies produced from engineered cell lines. Such cell lines will have been engineered to express the relevant antibody gene. The antibody gene may either be a human gene or a gene from another species which has been humanised by modification of the native sequence to prevent rejection when administered to a human, e.g. a humanised recombinant antibody. The antibody is preferably an antibody directed against the human T cell surface receptor TCR V β 5.2/5.3 (the method for constructing such an antibody is described in WO 95/16038 and the description of such methods is hereby incorporated by reference), and is more preferably an IgG, IgG1 or IgG/ κ . The antibody is most preferably the antibody produced by the cell line deposited on June 22, 1995 under the Budapest treaty as ATCC (CRL 11949) [herein this antibody is referred to as 'TM27'] or is one comprising the following TM27 V κ sequence:

1 DIQMTQSPSSLSASVGDRVITITCSASQGISNYLNWYQQTPGKAPKLLIYY 50

51 TSSLHSGVPSRFSGSGSGTDYFTFTISLQPEDLATYYCQQYSKLPRTFGQ 100

5

101 GTKLQIT 107,

and further comprises an amino acid sequence selected from the group consisting of the
TM27 VH amino acid sequence:

10

1 QVQLQESGPGGLVRPSQTLSTCTVSGFSLTAYGVNWVRQPPGRGLEWLGM 50

51 IWGDGNTDYN SALKSRVTMLKDT SKNQFSLRLSSVTAADTAVYYCARDRV 100

15

101 TATLYAMDYWGQGSLVTVSS 120,

the TM27 VH sequence wherein amino acid residue 48 is replaced with isoleucine (I),

the TM27 VH sequence wherein amino acid residues 78 and 79 are valine (V) and
phenylalanine (F),

20

the TM27 VH sequence above wherein amino acid residues 67 to 70 VTML are replaced
with LSIS respectively and amino acid 73 is an asparagine (N),

25

the TM27 VH sequence wherein amino acid residue 92 is an arginine (R).

The present invention also provides for the use of formulations of the present invention in
medical therapy and particularly for the treatment of autoimmune disease and further
particularly in the therapy of multiple sclerosis.

30

In preferred embodiments of the present invention the formulation has a pH in the range 5.5 to 6.5 and is most preferably pH 5.5. The pH may be altered using any pharmaceutically acceptable acid or alkali.

- 5 The formulation of the present invention may be prepared under aseptic conditions, leading to a sterile formulation.

The invention will now be illustrated by reference to the following examples which are in no way intended to be limiting of the scope of the invention described herein.

EXAMPLES

The antibody assayed in the following examples is TM27 which is a humanised antibody
5 (IgG1) produced in Chinese hamster ovary (CHO) cells by recombinant technology.

The bulk batches of TM27 used were purified by protein-A affinity chromatography.
The TM27 preparations were prepared from two different TM27 bulk solutions. One was
10.8 mg TM27 /ml in 10 mmol/l citrate buffer pH 5.5 and the other was 11.0 mg TM27 /ml
10 in 10 mmol/l phosphate buffer pH 6.5. The bulk solutions had sodium chloride added to
make them isotonic.

The TM27 preparations used in this study were prepared under aseptic conditions. The
batches were protected from air with nitrogen during the manufacturing and filling
15 processes. Eight batches with different compositions were prepared using the buffers
described.

For manufacturing purposes, TM27 bulk solution was diluted with the appropriate buffer to
a concentration of 1 mg/ml TM27 by gentle mixing, while avoiding foaming. The
20 manufactured solutions were filtered through a sterile 0.22 µm MILLEX-GV filter directly
into 10 ml sterile glass vials. Filling was performed from the bottom of the vials under
nitrogen protection.

The solutions were filled into 10 ml injection vials of neutral Type I glass (Ph Eur), 1
25 ml/vial. Bromobutyl rubber stoppers (FM 257) were used and the vials were sealed with
aluminium capsules.

The batches were stored under the following conditions: +5 °C/ambient humidity and +25
°C/30 % relative humidity. All the vials were stored upright. All examples contain
30 antibody at 1 mg/ml.

<u>Example 1: 10mmol/l citrate, pH 5.5</u>	<u>amount (mg)</u>
Citric acid monohydrate for parenteral use	0.387
Sodium citrate dihydrate for parenteral use	2.400
5 Sodium chloride for aseptic preparation	8.4
Water for injection	to 1 ml

Example 2: 5 mmol/l citrate ,pH 5.5

Citric acid monohydrate for parenteral use	0.194
Sodium citrate dihydrate for parenteral use	1.200
Sodium chloride for aseptic preparation	8.69
Water for injection	to 1 ml

Example 3: 8 mmol/l citrate, pH 5.5

Citric acid monohydrate for parenteral use	0.310
Sodium citrate dihydrate for parenteral use	1.920
Sodium chloride for aseptic preparation	8.52
Water for injection	to 1 ml

Example 4: 12 mmol/l citrate, pH 5.5

Citric acid monohydrate for parenteral use	0.464
Sodium citrate dihydrate for parenteral use	2.88
Sodium chloride for aseptic preparation	8.28
Water for injection	to 1 ml

Example 5: 15 mmol/l citrate, pH 5.5

Citric acid monohydrate for parenteral use	0.581
Sodium citrate dihydrate for parenteral use	3.600
Sodium chloride for aseptic preparation	8.11
Water for injection	to 1 ml

Example 6: 18 mmol/l citrate, pH 5.5

Citric acid monohydrate for parenteral use	0.697
Sodium citrate dihydrate for parenteral use	4.320
Sodium chloride for aseptic preparation	7.93
Water for injection	to 1 ml

Example 7: 20 mmol/l citrate, pH 5.5

Citric acid monohydrate for parenteral use	0.774
Sodium citrate dihydrate for parenteral use	4.800
Sodium chloride for aseptic preparation	7.82
Water for injection	to 1 ml

Example 8 (pH 5.5)

Citric acid monohydrate for parenteral use	0.387 mg
Sodium citrate dihydrate for parenteral use	2.400 mg
5 Sodium chloride for aseptic preparation	8.4 mg

Polysorbat 80 (Tween 80)

0.2 mg

Water for injection

to 1 ml

- 5 The formulations were studied over a 24 month period.

The results clearly showed that storage temperature, buffer composition and pH influence the stability of TM27. The best stability is achieved at low storage temperature (+5 °C).

- 10 The formulations exemplified in examples 1-7 were stable for 24 months whereas the formulation in example 8 was stable for 12 months.

CLAIMS.

1. An isotonic pharmaceutical formulation comprising an IgG antibody and a buffer,
5 wherein the antibody is present at from 0.5 mg/ml to 10 mg/ml, the buffer is a citrate
 buffer present at 5mmol/l to 20mmol/l and the pH of the formulation is 5.3 to 7.2.
2. A formulation according to claim 1, wherein the pH is 5.5 to 6.5.
- 10 3. A formulation according to claim 1, wherein the pH is 5.5.
4. A formulation according to any one of claims 1 to 3, wherein the citrate is present at
 7.5mmol/l to 15mmol/l .
- 15 5. A formulation according to any one of claims 1 to 4, wherein the citrate is present at
 10mmol/l.
6. A formulation according to any one of claims 1 to 5, wherein the antibody is an IgG1.
- 20 7. A formulation according to claim 6, wherein the antibody is an IgG1/ κ .
8. A formulation according to any one of the preceding claims, wherein the antibody is a
 recombinant antibody.
- 25 9. A formulation according to claim 8, wherein the antibody is a humanised recombinant
 antibody.
10. A formulation according to claim 9, wherein the antibody is directed against the human
 T cell surface receptor TCR V β 5.2/5.3.

11. A formulation according to claim 10, wherein the antibody is produced by the cell line with the deposition number CRL 11949.

12. A formulation according to claim 11, wherein the antibody comprises the TM27 V κ amino acid sequence:

1 DIQMTQSPSSLSASVGDRVTITCSASQGISNYLNWYQQTPGKAPKLLIYY 50

51 TSSLHSGVPSRFSGSGSGTDYFTISSLPEDIATYYCQQYSKLPRTFGQ 100

101 GTKLQIT 107,

and further comprises an amino acid sequence selected from the group consisting of the TM27 V H amino acid sequence:

1 QVQLQESGPGGLVRPSQTLSTCTVSGFSLTAYGVNWVRQPPGRGLEWLGM 50

51 IWGDGNTDYN SALKSRVTMLKDTSKNQFSLRLSSVTAADTAVYYCARDRV 100

101 TATLYAMDYWGQGSLVTVSS 120,

the TM27 V H sequence wherein amino acid residue 48 is replaced with isoleucine (I),

the TM27 V H sequence wherein amino acid residues 78 and 79 are valine (V) and phenylalanine (F),

the TM27 V H sequence above wherein amino acid residues 67 to 70 VTML are replaced with LSIS respectively and amino acid 73 is an asparagine (N),

the TM27 V H sequence wherein amino acid residue 92 is an arginine (R).

13. An isotonic pharmaceutical formulation comprising the antibody TM27 and a buffer,
wherein the antibody is present at 0.5 mg/ml to 10 mg/ml, the buffer is a citrate buffer
5 present at 5mmol/l to 20mmol/l and the pH of the formulation is 5.3 to 7.2.
14. A formulation according to any one of claims 1 to 13, which is a sterile formulation.
15. A process for the preparation of an isotonic pharmaceutical formulation according to
10 any one of claims 1 to 14, comprising incorporation of the antibody in an isotonic
medium wherein the antibody is present at from 0.5 mg/ml to 10 mg/ml, the buffer is a
citrate buffer present at 5mmol/l to 20mmol/l and the pH of the formulation is 5.3 to
7.2.
16. A formulation according to any one of the previous claims, for use in medical therapy.
17. A formulation according to any one of claims 1 to 14, for use in the therapy of an
autoimmune disease.
18. A formulation according to any one of claims 1 to 14, for use in the therapy of multiple
20 sclerosis.
19. Use of a formulation according to any one of claims 1 to 14, in the preparation of a
medicament for use in the therapy of an autoimmune disease.
20. Use of a formulation according to any one of claims 1 to 14, in the preparation of a
medicament for use in the therapy of multiple sclerosis.
21. A method for improving the storage of an antibody comprising formulating the
30 antibody in a formulation as claimed in any one of claims 1 to 14.

22. A method according to claim 21, wherein the formulation is stored at a temperature between 4°C and 10°C.
- 5 23. A method according to claim 22, wherein the temperature is 5°C.

SEQUENCE LISTING

<110> Lundquist, Tomas

<120> Sequence Listing

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<140> 00/000,000

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<170> PatentIn Ver. 2.0

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<213> Artificial Sequence

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<223> Description of Artificial Sequence:humanized

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<400> 1

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Gln Gly Ile Ser Asn Tyr

20 25 30

Leu Asn Trp Tyr Gln Gln Thr Pro Gly Lys Ala Pro Glu Leu Leu Ile

35 40 45

Tyr Tyr Thr Ser Ser Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr Ile Ser Ser Leu Gln Pro

65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Lys Leu Pro Arg

85

90

95

Thr Phe Gly Gln Gly Thr Lys Leu Gln Ile Thr

100

105

<210> 2

<211> 120

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<213> Artificial Sequence

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<223> Description of Artificial Sequence:humanized

monoclonal antibody

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Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Arg Pro Ser Gln

1

5

10

15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ala Tyr

20

25

30

Gly Val Asn Trp Val Arg Gln Pro Pro Gly Arg Gly Leu Glu Trp Leu

35

40

45

Gly Met Ile Trp Gly Asp Gly Asn Thr Asp Tyr Asn Ser Ala Leu Lys

50

55

60

Ser Arg Val Thr Met Leu Lys Asp Thr Ser Lys Asn Gln Phe Ser Leu

65

70

75

80

Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala

85

90

95

Arg Asp Arg Val Thr Ala Thr Leu Tyr Ala Met Asp Tyr Trp Gly Gln

100

105

110

Gly Ser Leu Val Thr Val Ser Ser

115

120

<210> 3

<211> 120

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence:humanized
monoclonal antibody

<400> 3

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Arg Pro Ser Gln

1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ala Tyr

20 25 30

Gly Val Asn Trp Val Arg Gln Pro Pro Gly Arg Gly Leu Glu Trp Ile

35 40 45

Gly Met Ile Trp Gly Asp Gly Asn Thr Asp Tyr Asn Ser Ala Leu Lys

50 55 60

Ser Arg Val Thr Met Leu Lys Asp Thr Ser Lys Asn Gln Phe Ser Leu

65

70

75

80

Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala

85

90

95

Arg Asp Arg Val Thr Ala Thr Leu Tyr Ala Met Asp Tyr Trp Gly Gln

100

105

110

Gly Ser Leu Val Thr Val Ser Ser

115

120

<210> 4

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:humanized

monoclonal antibody

<400> 4

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Arg Pro Ser Gln

1

5

10

15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ala Tyr

20

25

30

Gly Val Asn Trp Val Arg Gln Pro Pro Gly Arg Gly Leu Glu Trp Leu

35

40

45

Gly Met Ile Trp Gly Asp Gly Asn Thr Asp Tyr Asn Ser Ala Leu Lys

50

55

60

Ser Arg Val Thr Met Leu Lys Asp Thr Ser Lys Asn Gln Val Phe Leu

65

70

75

80

Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala

85

90

95

Arg Asp Arg Val Thr Ala Thr Leu Tyr Ala Met Asp Tyr Trp Gly Gln

100

105

110

Gly Ser Leu Val Thr Val Ser Ser

115

120

<210> 5

<211> 120

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence:humanized

monoclonal antibody

<400> 5

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Arg Pro Ser Gln

1

5

10

15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ala Tyr

20

25

30

Gly Val Asn Trp Val Arg Gln Pro Pro Gly Arg Gly Leu Glu Trp Leu

35

40

45

Gly Met Ile Trp Gly Asp Gly Asn Thr Asp Tyr Asn Ser Ala Leu Lys

50

55

60

Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Asn Gln Phe Ser Leu

65

70

75

80

Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala

85

90

95

Arg Asp Arg Val Thr Ala Thr Leu Tyr Ala Met Asp Tyr Trp Gly Gln

100

105

110

Gly Ser Leu Val Thr Val Ser Ser

115

120

<210> 6

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:humanized

monoclonal antibody

<400> 6

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Arg Pro Ser Gln

1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ala Tyr

20 25 30

Gly Val Asn Trp Val Arg Gln Pro Pro Gly Arg Gly Leu Glu Trp Leu

35 40 45

Gly Met Ile Trp Gly Asp Gly Asn Thr Asp Tyr Asn Ser Ala Leu Lys

50 55 60

Ser Arg Val Thr Met Leu Lys Asp Thr Ser Lys Asn Gln Phe Ser Leu

65 70 75 80

Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Arg Tyr Tyr Cys Ala

85

90

95

Arg Asp Arg Val Thr Ala Thr Leu Tyr Ala Met Asp Tyr Trp Gly Gln

100

105

110

Gly Ser Leu Val Thr Val Ser Ser

115

120

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/00049

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 39/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, BIOSIS, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9311794 A1 (XOMA CORPORATION), 24 June 1993 (24.06.93), See especially page 34, lines 3-15	1,2,4,5, 14-21
Y	--	1-18
Y	WO 9516038 A2 (T CELL SCIENCES, INC.), 15 June 1995 (15.06.95), See especially abstract, claim 2 and page 60, lines 1-24	6-10,12-13, 17-20
Y	WO 9011091 A1 (CENTOCOR, INC.), 4 October 1990 (04.10.90), See abstract and claims 1-3	1-18
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☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search

31 March 1999

Date of mailing of the international search report

20 -04- 1999

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/00049

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0531539 A1 (MITSUI TOATSU CHEMICALS, INC.), 17 March 1993 (17.03.93), See claims 2 and 3 --	1,2
A	WO 8911298 A1 (CENTOCOR, INC.), 30 November 1989 (30.11.89) -- -----	

Information on patent family members

International application No.

02/03/99

PCT/SE 99/00049

Form PCT/ISA/210 (patent family annex) (July 1992)

Information on patent family members

International application No.

PCT/SE 99/00049

Form PCT/ISA/210 (patent family annex) (July 1992)